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Acceleration of bromide mediated benzoylperoxide oxidations of secondary alcohols in aqueous organic solvents

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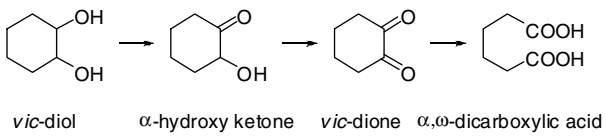
Abstract

The efficiency of the bromide mediated benzoylperoxide oxidation of 2° alcohols to ketones was greatly improved by the addition of water. The aqueous oxidation protocol allows also the direct use of off-the-shelf benzoylperoxide reagent without an otherwise necessary and potentially dangerous drying procedure. The oxidation of cyclopentanol, cyclohexanol, 1-phenyl-ethanol and three menthol isomers occurred in good to excellent yields. The oxidation reaction tolerated *N*,*N*-dimethylacetamide (DMA) as the solvent, which resulted in a slightly lower oxidation rate than acetonitrile. Chemoselective oxidation of vicinal diols to α-hydroxy ketones did not succeed under the aqueous organic conditions employed as over-oxidation and bromination side-reactions were observed. The impact of water content, solvent, oxidant source and type of alcohol substrates employed was investigated.

Keywords: Hypobromous acid; Benzoyl hypobromite; Selective oxidation; Mechanistic studies; Vicinal diol

1. Introduction

α-Hydroxy ketones (α-ketols) are an important functional group in natural products[1–3] and have been synthesized by many different methods.[4] However, only little is known about the selective oxidation of vicinal diols to α-hydroxy ketones as over-oxidation to *vic*-diones and carboxylic acids is thermodynamically favoured (Scheme 1). We reported earlier the effectiveness and the chemoselectivity of Ishii's $NaBrO_3/NaHSO_3$ reagent for the oxidation of *vic*-diols to α-hydroxy ketones.[5,6] This remarkable method generates the active oxidant hypobromous acid, HOBr, at a low concentration that is steadily replenished through a cascade of comproportionation and disproportionation reactions.[6]



Scheme 1. Oxidation of *cis*-/*trans*-1,2-cyclohexanediol.

Doyle et al. reported a mild method for the oxidation of sterically hindered 2° alcohols to ketones by a bromide mediated benzoylperoxide (Bz_2O_2) oxidation mechanism generating benzoyl hypobromite, PhC(O)OBr, as the oxidant.[7–11] In the presence of nickel(II) salts, the method exhibited excellent regioselectivity for the oxidation of 2,2-disubstituted-1,4-butanediols to γ-lactones by the formation of a seven-membered nickel(II)-1,4-butanediol complex intermediate.[8] These results prompted us to examine Doyle's method for the oxidation of 2° alcohol functions of *vic*-diols under polar, aprotic conditions, which we considered potentially interesting for the synthesis of usoliduloses ('oxo'-sugars) in which a 2° alcohol is oxidized to a carbonyl group.[12–17] Here, we report an improvement on and mechanistic insights into Doyle's bromide mediated peroxide oxidation method of alcohols.

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2. Results and discussion

Doyle's oxidation method was studied for cyclic 2° alcohols such as cyclopentanol and cyclohexanol, which were employed as simple furanose and pyranose sugar model systems. In anhydrous acetonitrile medium at 60 °C, complete conversion to cyclopentanone and cyclohexanone was detected by GC after 17 h and 12 h reaction time, respectively. A dramatic increase of the reaction rate was discovered when wet Bz_2O_2 was used instead of anhydrous Bz_2O_2. Commercially available benzoylperoxide contains approximately 30 wt % water and requires the removal of the water by an appropriate drying method.[18] (*Caution*—Drying of Bz_2O_2 can cause dangerous explosions and should only be conducted on a small scale.) After 1 h reaction time, the oxidation reaction of cyclohexanol had a cyclohexanone content of 38%, detected by GC, when wet Bz_2O_2 was used, compared to 18% under anhydrous conditions. The water content of 432 mg of wet benzoylperoxide (30 wt % water) in 6.5 mL of acetonitrile gave a 1.1 vol % aqueous acetonitrile solution. The influence of the water was thus investigated by varying the water content of acetonitrile solutions (Table 1). A 20 vol % and 30 vol % water content resulted in 95% and 98% cyclohexanone yields after only 1 h at 60 °C, that is, a more than 10-fold acceleration compared to the anhydrous condition. Additional water, however, decreased the yield. Oxidation in water only, that is, in absence of acetonitrile, was not possible due to the insolubility of benzoylperoxide in water. The water content–ketone yield correlation can be explained by an acceleration of the reaction rate with water: The steep initial increase reaches a maximum at around 30 vol % water as benzoylperoxide becomes less soluble in the solvent mixture, which results in an overall decline in the reaction rate by either a reduction of the effective concentration of benzoylperoxide or a change in the reaction mechanism. The large increase in reaction rate from 1.5 vol % to 20 vol % and the little increase from 20 vol % to 30 vol % is an indication that the reaction rate is concentration dependent at low water levels and is little affected once an elevated water content has been reached.

In order to oxidize carbohydrates CH_3CN was changed to *N*,*N*-dimethylacetamide (DMA).[19,20] Aprotic, polar solvents, such as DMA, are uniquely suited to dissolve partially protected sugars and free monosaccharides. 1-Phenyl-ethanol, cyclopentanol and cyclohexanol were oxidized to the corresponding ketones in DMA after 24 h at 60 °C in 92%, 74% and 80%, respectively. The lower reaction rate in DMA relative to acetonitrile is presumably due to increased peroxide deactivation, which is more prominent in solvents with higher polarity, by the loss of CO_2 via pathways of carboxy inversion and subsequent side reactions.[21] In order to decrease the thermal decomposition of Bz_2O_2, the oxidation of 1-phenyl-ethanol was carried out at ambient temperature. In DMA and acetonitrile solvent, the oxidation rate is very slow at ambient temperature with only 10% acetophenone product after 48 h. Quantitative conversions were confirmed by GC after 12 h when a second addition of 1.5 equiv of Bz_2O_2 had been added after 6 h.[22,23] We also conclude that the acceleration of the oxidation reaction is not a solvent effect as similar reactivity profiles have been observed in different solvents, DMA and CH_3CN, only in the presence of water.

Further insights into the oxidation mechanism were obtained by a series of experiments varying nickel salts, oxidants and substrates. Nickel salts with various counter ions were investigated for the oxidation of cyclohexanol as Ni^{2+} influenced the regioselectivity of the oxidation of 2,2-disubstituted-1,4-butanediols to γ-lactones dramatically.[7,8] The reactions were conducted with 2.5 equiv of Bz_2O_2 in 20 vol % aqueous acetonitrile solvent at 60 °C and were monitored by GC. A snapshot of the cyclohexanone content after 2 h was chosen in order to compare the influences of the nickel salts. No oxidation products were detected when the nickel salts lacked halogenides, that is, $NiSO_4$, $Ni(NO_3)_2$, $Ni(ClO_4)_2$, $Ni(OAc)_2$ and NiO_2.[24] The best result was obtained with $NiBr_2$ with a 47% cyclohexanone content after 2 h. $NiBr_2(PPh_3)_2$ showed a slightly decreased oxidation activity, 37% cyclohexanone after 2 h, presumably by the interference of triphenyl phosphine or by reduced Ni–Br dissociation, thereby lowering the effective bromide ion concentration. The presence of triphenyl phosphine also interfered with the isolation of the ketones. $NiCl_2$ and NiI_2 produced a cyclohexanone content of 23% and 20% after 2 h.

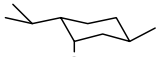
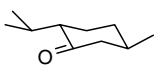
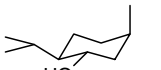
Table 2 lists the result of the oxidation of 2° alcohols in DMA. Cyclohexanol was oxidized completely to cyclohexanone within 1 h, while cyclopentanol required 3 h for quantitative oxidation. The investigation of steric influences in a series of the menthol isomers showed that the oxidation of neomenthol was completed after 1 h, while the menthone and isomenthone contents produced for menthol and isomenthol were 65% and 36% yields. There was a clear preference for the oxidation of OH in axial versus equatorial positions as the reactivity decreases from neomenthol > menthol > isomenthol. This reactivity effect

Table 1
Influence of water content on the oxidation of cyclohexanol[a]

Entry	Volume of H_2O (mL)	Volume of CH_3CN (mL)	vol % of water	Cyclohexanone content[b] after 1 h (%)
1	—	6.5	—	18
2[c]	0.1	6.4	1.5	38
3	1.3	5.2	20	95
4	2.0	4.5	30	98
5	3.25	3.25	50	83
6[d]	6.5	—	100	0

[a] Cyclohexanol (0.50 mmol, 100 mg), anhydrous benzoylperoxide (1.25 mmol, 303 mg) and $NiBr_2$ (0.125 mmol, 27.4 mg) in 6.5 mL at 60°C.
[b] Determined by GC; calibrated against methyl sulfone as internal standard. Typical error range less than ±2%.
[c] The result was identical to a 1.1 vol % solution with wet benzoyl-peroxide (1.25 mmol, 432 mg wet Bz_2O_2, 30 wt % water) in 6.5 mL of dry CH_3CN.
[d] Vigorous stirring of the reaction mixture.

Table 2
Oxidation of secondary alcohol substrates[a]

Entry	Reactant	Product	Yield after 1 h (%)	Yield after 3 h (%)
1	Cyclohexanol	Cyclohexanone	100	—
2	Cyclopentanol	Cyclopentanone	23	100
3	1-Phenyl-ethanol	Acetophenone	94	100
4	 (+)-menthol	 (−)-menthone	65	86
5	 (+)-neomenthol	 (−)-menthone	100	—
6	 (+)-isomenthol	 (+)-isomenthone	36	46

[a] Alcohol (1.0 mmol), $NiBr_2$ (0.25 mmol), wet Bz_2O_2 (2.5 mmol) in 6.5 mL of DMA at 60 °C with dimethyl sulfone as internal GC standard.

can be explained by a preferential attack of the oxidant, benzoyl hypobromite or hypobromous acid (vide infra), of an equatorial C–H of the 2° alcohol, that is, an axial OH group, as the hydrogen is less sterically shielded by 1,3-diaxial interactions (Fig. 1). The bulky isopropyl group of the menthol isomers influences the conformation of the cyclohexane ring and thus directs the hydroxyl group to an equatorial position in menthol, to an intermediate equatorial–axial position in isomenthol and to an axial position in neomenthol affecting the oxidation rates of the respective isomer. The activated benzylic C–H group in 1-phenyl-ethanol was less favoured for the oxidant attack than the aliphatic equatorial C–H in neomenthol. A similar oxidation reactivity profile has been obtained for the menthol series with the $NaBrO_3/NaHSO_3$ reagent.[6]

cis- and trans-Configurations of 1,2-cyclohexanediol and 1,2-cyclopentanediol were oxidized in 20 vol % aqueous DMA at 60 °C. The oxidations of *vic*-diols resulted in unselective side reactions as a multitude of compounds were observed by GC. GC–MS analysis confirmed the presence of monobrominated compounds based on the characteristic M and M+2 *m*/*z* signal pattern for bromine isotopes. However, it was impossible to identify the products of these complex reaction mixtures. The brominated compounds had molecular masses that indicated a formal

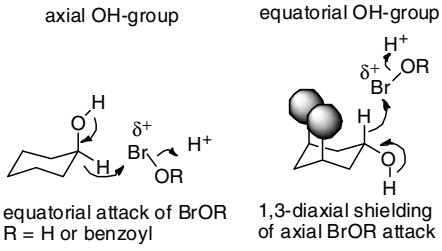
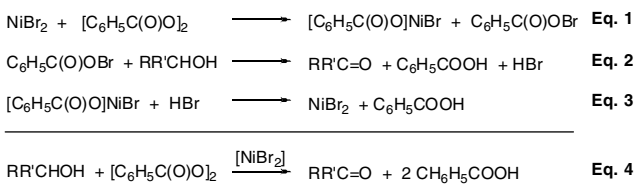


Fig. 1. Proposed equatorial versus axial attack of BrOR (R = H or benzoyl).

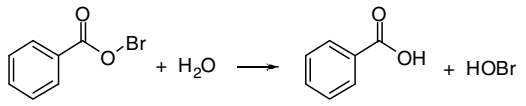
substitution of OH with Br. The presence of Bz_2O_2 could allow a Prevost type reaction mechanism in which a hydroxy group is substituted by a halogenide via a benzoyl-ester intermediate.[25] In an attempt to decrease the amount of brominated by-products the reaction temperature was lowered from 60 °C to room temperature slowing the oxidation reaction, however, the amounts of brominated compounds generated did not change further suggesting that they are formed through radical processes with low activation barriers.

The sugar substrates methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, phenyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl 4,6-*O*-isopropylidene-D-mannopyrannoside were tested in aqueous DMA at 60 °C. After work-up, the product mixtures had a syrupy consistency, and an intractable mixture of a multitude of products was detected by NMR that indicates non-selective decomposition of the sugars. The decomposition of the sugar compounds can be caused by thermal stress, low pH generated by the benzoic acid products and side reactions of oxidant. Attempts to increase the chemoselectivity by buffering of the reaction mixture with Na_2HPO_4 failed as again only decomposition products could be detected. The modified Doyle's oxidation method is therefore only suitable for simple 2° alcohols.

Doyle proposed that the oxidation is based on the formation of benzoyl hypobromite, which is generated by the reaction of bromide with Bz_2O_2 (Scheme 2).[7,8] Although the stoichiometry of the reaction is known, the actual oxidation mechanism of the reaction of benzoyl hypobromite with a 2° alcohol is not well understood. It is assumed that a formal Br^+ cation, or the positively charged Br in benzoyl hypobromite, attacks the geminal C–H of the 2° alcohol (Fig. 1). A detailed investigation of the formation of benzoyl hypobromite as intermediate in anhydrous acetonitrile in the presence of 18-crown-6 ether and KBr was reported by Opeida et al.[26] Bunce et al. reported that the related benzoyl hypochlorite was very sensitive towards water as it quenched a radical reaction pathway through the hydrolysis.[27,28] Based on the results of the studies involving nickel salts, oxidant sources, water content and solvent we would like to postulate that the rate acceleration under wet conditions is based on the in situ generation of hypobromous acid, HOBr, which is generated by the hydrolysis of the benzoyl hypobromite intermediate (Scheme 3). An explanation for the acceleration of the oxidation rate is the smaller size of HOBr and the greater polarization of $Br^{\delta+}$ in HOBr compared to



Scheme 2. $NiBr_2$ mediated Bz_2O_2 oxidation of a 2° alcohol.



Scheme 3. Hydrolysis of benzoyl hypobromite to generate the proposed actual oxidant HOBr.

benzoyl hypobromite. Thus, HOBr can more easily attack the geminal C–H of the 2° alcohol group (Fig. 1).

3. Conclusion

The utility of the $NiBr_2$ mediated benzoylperoxide method for the oxidation of 2° alcohols to ketones was substantially improved by the addition of water. The aqueous oxidation protocol allows the direct use of commercially available benzoylperoxide off-the-shelf without a potentially dangerous drying procedure and also results in shorter reaction times. The modified oxidation method tolerates also DMA solvent, however, the oxidation proceeds at a slightly slower rate than in acetonitrile. The oxidation of vicinal-diol compounds failed as over-oxidation and bromination side reactions were observed.

4. Experimental

NMR spectra (400 MHz/^{1}H; 100 MHz/^{13}C) were measured in deuterated chloroform (δ 7.24, ^{1}H; δ 77.0, ^{13}C) as the internal reference. GC analyses were performed on a 30 m × 0.25 mm PEG column. The GC-FID was calibrated for cyclohexanol, cyclopentanol, *cis*- and *trans*-1,2-cyclohexanediol, *cis*- and *trans*-1,2-cyclopentanediol, α-hydroxy cyclohexanone and 1,2-cyclohexadione with dimethyl sulfone as an internal standard. All chemicals were purchased from commercial sources and were reagent grade and used as obtained without further purification unless otherwise noted. Oil-pump vacua applied in the isolation of the ketones were ⩽30 mTorr. *Caution*: The handling of solid peroxides—particularly anhydrous—can lead to potential explosions.[18] All experiments should be performed in a fume hood. Excess peroxide is to be destroyed with aqueous saturated sodium thiosulfate solution.[18]

4.1. General procedure for small-scale oxidations

In an 8 mL screw top vial, alcohol (0.50 mmol), nickel(II)bromide (0.25 mmol = 0.50 equiv with respect to available bromide and alcohol, 54 mg) and dimethyl sulfone (~50 mg) were dissolved in 5.2 mL DMA or CH_3CN and 1.3 mL water at 60 °C. The reactions were conducted in air. After the addition of solid benzoyl peroxide (Bz_2O_2; 1.25 mmol, 303 mg) the reaction mixture is stirred at 60 °C for 1–24 h and monitored by GC analysis of the crude reaction mixture. After completion, the reaction mixture is quenched with 10 mL of 1.0 M sodium thiosulfate/2 M $NaHCO_3$ solution and the aqueous layer is extracted by 3 × 20 mL of diethyl ether. The combined organic layers were washed with 25 mL of brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure.

4.2. General procedure for large scale oxidations

In a 100 mL round-bottom flask, alcohol (2.0 mmol) benzoylperoxide (5 mmol, 1.21 g) and nickel(II)bromide (1.0 mmol, 218 mg) in 5 mL of water and 20 mL of DMA or CH_3CN were stirred at 60 °C. After completion, the reaction mixture is quenched with 30 mL 1.0 M sodium thiosulfate/2 M $NaHCO_3$ solution and the aqueous layer is extracted with 3 × 50 mL diethyl ether. The combined organic layers were washed with 50 mL brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Without further purification, the ketone products were characterized by GC–MS and NMR spectroscopy and found to be congruent to literature values.

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Supplementary data

Supplementary data (additional oxidant source studies, CAS registry numbers of organic compounds and IR spectroscopic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.098.

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